

Zeolites as Catalysts in the Fischer Indole Synthesis. Enhanced Regioselectivity for Unsymmetrical Ketone Substrates

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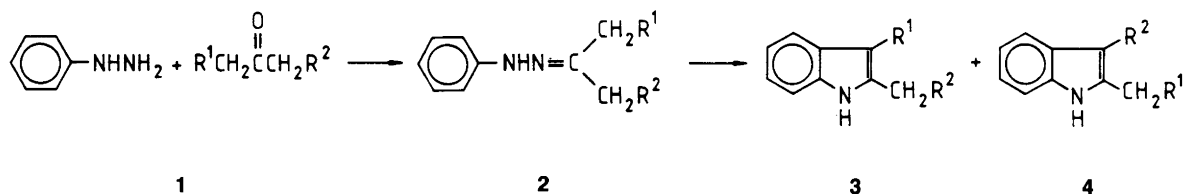
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The use of zeolites as catalysts in the Fischer indole synthesis has been studied on five unsymmetrical ketone substrates with 14 different zeolites. Both the corresponding phenylhydrazone and the parent ketone in the presence of phenylhydrazine were used as substrates. Zeolites which catalysed the indolization of the phenylhydrazones were also active in the direct conversion of the parent ketone. For substrates which gave mixtures of isomeric indoles under homogeneous, classical indolization conditions in acetic acid, it was found that the distribution of regioisomers of the indoles formed was altered considerably by zeolite catalysis and that the distribution was dependent on the type of zeolite used. A one-pot synthetic procedure for indole synthesis from the parent ketone and phenylhydrazine is described.

Formation of indoles by acid catalysed rearrangement of arylhydrazones is known as the Fischer indole reaction. With hydrazones obtained from unsymmetrical ketones, possessing both α and α' methylene groups, two isomeric indoles can be formed (Scheme 1).

Many attempts to increase the regioselectivity of the reaction by varying the acid catalyst and/or the solvent composition have been described in the literature.¹ In a recent paper² we described a multivariate study of the influence of the properties of the Lewis acid catalyst and of the solvent on the regioselectivity of the Fischer indole reaction for a series of unsymmetrical substrates. The results of this study were unexpected: the chemical properties of the Lewis acid catalyst do not have any influence at all on the regioselectivity; the solvent has only a weak influence. The dominant factor determining the regiochemistry is the steric bulk of the side chains of the parent ketone. Hence, one possibility of enhancing the selectivity would be to increase the effects of steric congestion by forcing the reaction to occur on or close to a suitably shaped solid

surface. For this purpose, zeolites appeared to us to be ideal candidates. Extensive reviews on the chemistry of zeolites have been published³ and we do not go into details here. The use of zeolites as catalysts in the Fischer indole reaction has previously been described.⁴ However, in this work only symmetrical phenylhydrazones were treated and the potential use of zeolites for selective transformation was not recognized. Zeolites may furnish another advantage since they contain channels in which small molecules can enter and be retained. Ammonia is liberated during the reaction and if it can be trapped in the channels of suitably tailored zeolites this would provide an extra driving force for the reaction. Since water can also be retained by zeolites, another possibility would be to condense the parent ketone and phenylhydrazine in the presence of zeolites and thereby establish a one-pot procedure for the synthesis of indoles from ketones. This paper summarizes our findings on the use of zeolites in the Fischer indole reaction with unsymmetrical ketone substrates.



Scheme 1.

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Materials, methods and results

Screening experiments: phenylhydrazones as substrates. To determine whether or not zeolites are capable of catalysing the indolization reaction, screening experiments were run in which the phenylhydrazones (**2a–e**) of five unsymmetrical ketones were treated with 14 different powdered zeolites suspended in refluxing cyclohexane. The ketones were 2-hexanone (**1a**), 3-hexanone (**1b**), 3-undecanone (**1c**), 1-phenyl-2-butanone (**1d**), and 5-methyl-3-heptanone (**1e**). Their selection was based on their principal properties⁵ and the ketones were the same as were used in Ref. 2. The zeolites were either commercial samples or research-type zeolites obtained as gifts from the manufacturer. The following zeolites were tested. Molecular sieves 3A, 4A, 5A (obtained from Janssen), and 13X (obtained from BDH Chemicals Ltd.). Zeolites M-5, M-8, Y-52, Y-72, Y-82, LZ 20, and KL were obtained from Union Carbide Co. Mordenite (H-form), Zeolite Y and ZSM-5 were obtained from Conteka B. V. The reactions were monitored by capillary GLC and the indole isomer distribution was determined from the integrated peak areas. The identities of the indole isomers were determined by GLC-MS and the mass spectra were identical with previously known spectra.² Although no precise yields were determined in these screening experiments, the conversion was evaluated qualitatively from the chromatograms and assigned as good (g), moderate (m) or poor (p) with regard to the amounts of indole products. The zeolites that afforded either good conversions and/or significantly altered regioselectivity were subsequently tested with xylene (mixture of isomers) as the solvent to allow the reaction to be carried out at higher temperature. Some of the zeolites were also tested in yet other solvents and toluene, 3-methylpentane and isooctane were also found to be useful. We actually tested a number of solvents uniformly spread in the principal property plot given in Ref. 6. However, solvents other than hydrocarbons gave side reactions. Although zeolites are also used for hydrocarbon cracking, the conditions used in the indolization reactions are obviously mild enough to avoid such side reactions.

A total of 112 different systems was tested in the screening experiments with the phenylhydrazones. The same zeolites and solvents were then tested along the same principles for one-pot reactions using equimolar mixtures of the ketones and phenylhydrazine as reactants. The results of these screening experiments were that the following combinations of substrate/zeolite were judged to merit more detailed studies: 3-hexanone / Mordenite, Zeolite Y; 1-phenyl-2-butanone / Mordenite, Zeolite Y; 3-undecanone / Mordenite, LZ-20; 2-hexanone / Mordenite, Y-82; 5-methyl-2-heptanone / Mordenite, Y-52.

It was found that zeolites which were active with the phenylhydrazone as the substrate were also active and gave indoles when the ketone and phenylhydrazine were used as substrates, although almost all zeolites afforded some transformation of ketones to phenylhydrazones.

Study of experimental conditions. There are many factors which could influence the result of the reaction, e.g. the relative amounts of ketone:phenylhydrazine; the amount of zeolite; the reaction temperature; the order of introduction of the reactants and the detailed conditions for this. To gain some control over the experimental conditions we used 3-hexanone/Mordenite and 3-hexanone/Zeolite Y as model systems and analysed the following factors by a two-level fractional factorial design, 2⁴. (A) the amount of zeolite:ketone; (B) the amount of solvent: ketone; (C) the stirring time of the zeolite in the presence of solvent prior to introduction of the ketone; (D) the stirring time of the zeolite + solvent + ketone prior to introduction of the phenylhydrazine. Other factors were maintained constant, i.e. a 1:1 molar ratio of ketone:phenylhydrazine; the mixing of the reactants was performed at room temperature; the reaction was run under reflux after the introduction of phenylhydrazine. The result of these experiments showed that the rate of conversion (and hence the yield) is dependent on the experimental conditions, whereas the distribution of indole isomers is not significantly influenced. The following levels of the factors were found to favour high conversion: (A) on a high level, a large amount of zeolite is favourable; (B) on a low level, a small amount of solvent ensures rapid adsorption of the reactants on the zeolite surface; (D) on a high level, which indicates that adsorption of the ketone on the zeolite surface is essential. The variation of factor (C) does not influence the yield.

Preparative runs. With the experimental conditions indicated above, we ran the reaction under preparative-scale conditions (20 mmol). The results are given in Table 1. For comparison, the isomer distributions obtained by indolization of the corresponding phenylhydrazone in acetic acid² are given in footnotes to Table 1. The reaction time given was determined from similar experiments in which the yield was monitored over 24 h by internal standard techniques by capillary GLC. In these experiments phenylcyclohexane was used as an internal standard. The yields given in Table 1 refer to isolated, distilled mixtures of indole isomers.

Desorption experiments. When the phenylhydrazones (in toluene solution) were added to zeolites they became adsorbed on the zeolite surface and disappeared from the solution as determined by GLC. The adsorbed phenylhydrazone could be desorbed by the addition of water to the mixture followed by prolonged heating. With **2a** 40–50% of the phenylhydrazone was liberated into the solution. With some zeolites the Fischer reaction occurred. The amounts of indoles in the solution with these systems were only slightly perturbed (within the analytical error of the GLC analysis, $\pm 2\%$) by this treatment which indicates that indoles are only weakly adsorbed onto the zeolites.

When toluene solutions of 3-hexanone and phenylhydrazine were refluxed in the presence of the following zeolites, molecular sieves 3A, 4A, 5A, 13X, Zeolites Y, ZMS-5, and

Table 1. Yields and distribution of indole isomers, 3a-e/4a-e, obtained in preparative runs.

Ketone	Zeolite	Reaction time/h	Ratio of indole isomers 3/4	Yield(%)
3-Hexanone (1a) ^a	Mordenite	5	10/90	85
	Zeolite Y	5	44/56	84
2-Hexanone (1b) ^b	Y-82	3	0/100	86
3-Undecanone (1c) ^c	Mordenite	5	4/96	83
	LZ-20	3	47/53	92
1-Phenyl-2-butanone (1d) ^d	Mordenite	4	93/7	82
	Zeolite Y	3	17/83	93
5-Methyl-3-heptanone (1e) ^e	Mordenite ^f	5	99/1	82

The following isomer ratios 3a-e/4a-e were observed in acetic acid. ^aA 20/80 ratio of 2,3-diethylindole/3-methyl-2-propylindole (3a/4a). ^bA 0/100 ratio of 2-butyldiole/2-methyl-3-propylindole (3b/4b). ^cA 29/71 ratio of 2-ethyl-3-heptyldiole/3-methyl-2-octylindole (3c/4c). ^dA 0/100 ratio of 2-benzyl-3-methylindole/2-ethyl-3-phenylindole (3d/4d). ^eA 100/0 ratio of 2-(2-methylbutyl)indole/3-(2-butyl)-2-ethylindole (3e/4e). ^fIsooctane was used as the solvent.

Mordenite, the formation of indoles was observed with Zeolite Y, ZMS-5 and Mordenite. From these reaction mixtures, no phenylhydrazone was liberated upon desorption treatment with water. From the 13X molecular sieves, 30–40% of phenylhydrazone was desorbed. The other types of molecular sieves did not yield any products. These results indicate that, with an active zeolite catalyst, the indolization step is rapid and that the formation of phenylhydrazone is rate limiting.

Discussion

Acid catalysis by zeolites can be effected either by Lewis acid sites (e.g. tri-coordinated Al) in the zeolite crystal framework, or by Brønsted acid sites (e.g. Al-OH) on the zeolite surface, or both. Which type of acid is responsible for the catalysis of the Fischer indole reaction is not discernible from the experiments described here. For practical purposes it really does not matter which. The results obtained show that our initial assumptions were correct in that a suitably shaped solid acid catalyst would enhance the regioselectivity of the indolization by amplifying the steric effects.

The selectivity is dependent on the type of zeolite used. For one substrate, 1-phenyl-2-butanone (1d), the selectivity is reversed on changing from Mordenite to Zeolite Y. For 3-hexanone (1a) and 3-undecanone (1c) the tendency is similar but less pronounced. This implies that, in addition to steric hindrance in the acid catalysis, different types of zeolites show a difference in specificity of the sites which bind the substrates to the zeolite crystals. However, we are not able to draw any conclusions concerning these intermediary interactions.

For two substrates, 2-hexanone (1b) and 5-methyl-3-heptanone (1e) zeolite catalysis does not offer any improvement with regard to selectivity compared with standard indolization in acetic acid or to the Lewis acid catalysed reaction since only one indole isomer is formed.

Since the selection of test substrates by their principal properties⁵ ensures a spread in the number of individual molecular properties, and since the reaction afforded high yields with all the substrates we conclude that the one-pot procedure given in this paper is likely to be a general indolization method.

Conclusions

An appropriate choice of zeolite affords a rapid indolization reaction from unsymmetrical ketones and phenylhydrazine. The reaction is more selective than that which can be accomplished in homogeneous solution, or with suspended Lewis acid catalysts. The facile experimental procedure, the high yields obtained, the low cost of zeolites (available in bulk quantities) will, hopefully, render the method described in this paper acceptable as a standard method for the Fischer indolization of ketones.

Experimental

Chemicals: The zeolites were activated by being heated at 200°C under reduced pressure (0.1 mmHg) for 5 h. The ketones were commercial *p.a.* or *puriss.* qualities purchased from Janssen and were used as delivered. The solvents were *p.a.* qualities and were dried over molecular sieves (4A).

GLC analyses. These run on a Carlo-Erba Fractovap 4160 equipped with an FID. A SPB-5 capillary column (0.30 mm i.d., 25 m) was used. Integrated peak areas were used to determine the isomer distribution and a Milton Roy C-10 integrator was employed. Yield determination in optimization experiments and in experiments to determine the reaction time was carried out by internal standard techniques using phenylcyclohexane as the internal standard.

GLC-MS analyses. These were run on a SIL-8 columns (0.21 mm i.d., 30 m) coupled to an HP GC/MSD 5830/5970 system. Electron impact, 70 eV, was used for ionization.

General procedure for screening experiments. The experiments were run in large (ground glass joint NS 19) test tubes equipped with a Liebig condenser and a guard tube containing calcium chloride. The zeolite, 1.00 g, was suspended in 10 ml of solvent and 5 mmol of the desired phenylhydrazone in 5 ml of solvent were added. In experiments to screen the one-pot procedure, 5 mmol of the ketone and 5 mmol of phenylhydrazine in 5 ml of solvent were added. The reaction mixture was heated at reflux temperature for 24 h and analysed by GLC.

Desorption experiments. These were run as above. After 24 h the heating was discontinued. The mixture was allowed to cool to just below 100°C and 25 ml of water were introduced. Stirring was continued and the organic layer was monitored by GLC. The desorption was considered complete when there were no further changes observed in the composition of the organic layer. In general 1 h was sufficient.

Fractional factorial experiments to determine experimental factors. These were run as above with xylene as the solvent and varying (A) the amount of zeolite (0.5–1.5 g); (B) the amount of solvent (5–15 ml); (C) the stirring time of the zeolite with the solvent prior to introduction of the reactants (5–60 min); (D) the stirring time of the mixture of zeolite and solvent with the ketone prior to introduction of the phenylhydrazine (5–60 min). An accurately weighed amount of phenylcyclohexane (internal standard), ca. 0.5 g, was added with the phenylhydrazine. The reaction mixture was refluxed for a total reaction time of 24 h although samples were withdrawn at intermediate times to monitor the reaction. The results obtained after 24 h were used for evaluation.

Procedure for preparative runs. The zeolite (6 g) was stirred with 40 ml of the solvent (xylene or isooctane) for 5 min whereafter 20 mmol of the ketone were added in one portion and the mixture was stirred for another 60 min. Phenylhydrazine (2.16 g, 20 mmol) was added in one por-

tion and the mixture was heated to reflux and the reaction allowed to proceed at reflux temperature for the time given in Table 1. After being cooled, the mixture was filtered through a sintered glass funnel and the solvent and unchanged ketone were removed by evaporation under reduced pressure (water aspirator). The residue was distilled under reduced pressure in a Kugelrohr apparatus. The following boiling points (Kugelrohr oven temperature) were recorded. Mixture of 2,3-diethylindole and 3-methyl-2-propylindole from 3-hexanone, b.p. 150–160°C/10 mmHg; 2-methyl-3-propylindole from 2-hexanone, b.p. 155–158°C/10 mmHg; mixture of 2-ethyl-3-heptylindole and 3-methyl-2-octylindole from 3-undecanone, b.p. 202–204°C/10 mmHg; mixture of 2-benzyl-3-methylindole and 2-ethyl-3-phenylindole from 1-phenyl-2-butanone, b.p. 210–220°C/10 mmHg; mixture of 3-methyl-2-(2-methylbutyl)indole and 3-(2-butyl)-2-ethylindole from 5-methyl-3-heptanone, b.p. 160–165°C/10 mmHg.

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